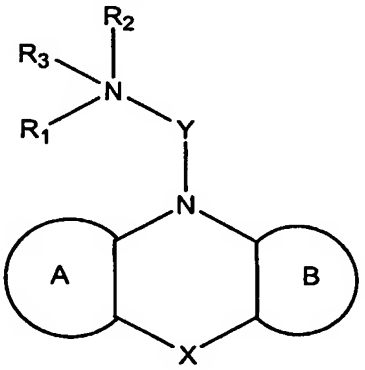
Claims

We claim:

1. A method of treating a patient with a *M. tuberculosis* infection comprising administering to the patient an amount of a composition comprising an electron transport chain inhibitor, wherein said amount is effective to inhibit the electron transport chain in said *M. tuberculosis* does not have anti-dopaminergic effects in said patient.

2. The method of claim 1 wherein said inhibitor is an oligonucleotide, a small molecule, a mimetic, a decoy, or an antibody.

3. The method of claim 1 wherein said inhibitor is a small molecule of formula I,



I

wherein:

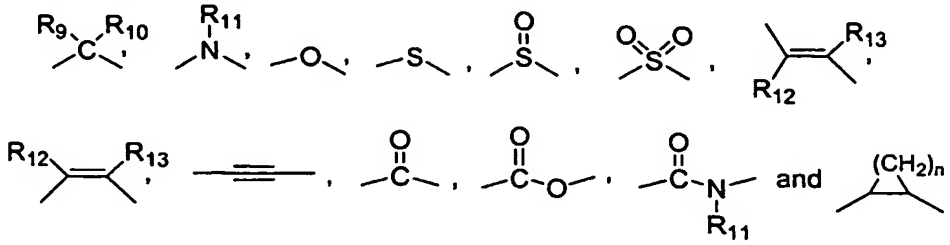
A and B are each independently aryl or heteroaryl and each are optionally substituted with 1-3 substituents selected from the group consisting of halogen, CHO, COR_4, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 alkoxy, phenyl (optionally substituted with 1-3 substituents selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, cyano, nitro, COOH, and CO_2R_4), heteroaryl (optionally substituted with 1-3 substituents selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, cyano, nitro, COOH, CO_2R_4), cyano, nitro, C_1-C_6 thioalkyl, C_1-C_6 thiohaloalkyl, C_1-C_6 alkylthiol, $(CH_2)_nCOOH$, $(CH_2)_nCO_2R_4$, $(CH_2)_nNR_5R_6$, $(CH_2)_nCONR_5R_6$, OH, SH, $(CH_2)_nNR_7COR_8$, $(CH_2)_nSOR_4$, SO_2R_4, $(CH_2)_nSONR_5R_6$, and $(CH_2)_nSO_2NR_5R_6$; and

n is an integer, wherein each n is independently selected from 0 to 6; and

R_4-R_8 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and phenyl (optionally substituted with from 1-3 substituents selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, cyano, nitro, COOH, CO_2Me); or

R_5 and R_6 together with the nitrogen they are attached form a 5 to 7 member ring; and

Y is a linker unit consisting of 1 to 6 atoms or atom groups wherein the atom or atom groups are selected from the following:



and R_9 through R_{13} are each independently selected from a group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and phenyl (optionally substituted with from 1-3 substituents selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, cyano, nitro, COOH, CO_2Me); and

R_1 and R_2 are each independently hydrogen, C_1-C_6 alkyl, $(CH_2)_nNR_4R_5$, phenyl (optionally substituted with 1-3 substituents selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, cyano, nitro, COOH, CO_2Me), CO_2R_4, $CO_2(CH_2)_n$phenyl (optionally substituted with from 1-3 substituents selected from halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, cyano, nitro, COOH, CO_2Me), C_1-C_6 haloalkyl, cycloalkyl (optionally substituted with from 1-3 substituents selected from NR_5R_6, halogen, and C_1-C_6 alkyl), heterocycloalkyl including 1-3 hetero ring atoms selected from NR_{11}, O and S, optionally substituted with 1-3 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, NO_2, CN, and $(CH_2)_nNR_4R_5$ or

R_1 and Y together with the nitrogen that they are attached form a 3 to 7 member ring; or

R_1 or R_2 together with the nitrogen that they are attached form a 3-7 member ring optionally containing from 1 to 3 additional heteroatoms selected from the group consisting of NR_{14}, O, and S, and optionally substituted with 1-3 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, NO_2, CN, and $(CH_2)_nNR_4R_5$; and

R_{14} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, SO_2R_4, $SO_2NR_5R_6$, $CO(CH_2)_n$phenyl (optionally substituted with 1-3 substituents selected from C_1-C_6 alkyl, NR_5R_6, NO_2), $(CH_2)_n$phenyl (optionally substituted with 1-3 substituents selected from C_1-C_6 alkyl, halogen, NH_2, OH, OR, NO_2), CO_2R_4; and

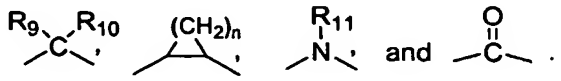
X is NR_{11}, O, S, SO, or SO_2; and

when both R_1 and R_2 are not hydrogen, R_3 is optionally present as H, C_1-C_6 alkyl, $(CH_2)_n$phenyl (optionally substituted with 1-3 groups selected from the group consisting of C_1-C_6 alkyl, halogen, NO_2, cyano, COOH, CO_2Me), or C_1-C_6 haloalkyl.

4. A method according to claim 3, wherein for the compound of formula I:

A and B are each aryl independently and optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_1-C_3 haloalkyl, C_1-C_3 thioalkyl, C_1-C_3 thiohaloalkyl, cyano, $SO_2NR_5R_6$, SO_2R_4 and C_1-C_6 alkoxy; and

Y is a linker unit consisting of 1 to 4 atoms or atom groups wherein the atom or atom group is selected from the following



5. A method according to claim 4 wherein each aryl is independently naphthyl or phenyl.

6. A method according to claim 4 wherein A and B are each phenyl and each phenyl is independently and optionally substituted with one substituent selected from halogen, CF_3, SMe, SCF_3, cyano, $SO_2N(Me)_2$, OMe, and SO_2Me; and

X is S or SO_2.

7. A method according to claim 6 wherein A is unsubstituted and B is substituted with Cl at the position para to X.

8. A method according to claim 6 wherein A is unsubstituted and B is substituted with CF_3 at the position para to X.

9. A method according to claim 6 wherein A is unsubstituted and B is substituted with SMe at the position para to X.

10. A method according to claim 6 wherein A is unsubstituted and B is substituted with SCF_3 at the position para to X.

11. A method according to claim 6 wherein A is unsubstituted and B is substituted with $SO_2N(Me)_2$ at the position para to X.

12. A method according to claim 6 wherein A is unsubstituted and B is substituted with OMe at the position para to X.

13. A method according to claim 6 wherein A is unsubstituted and B is substituted with cyano at the position para to X.

14. A method according to claim 6 wherein A is unsubstituted and B is substituted with SO_2Me at the position para to X.

15. A method according to claim 6 wherein Y is $(CH_2)_3$; and R_1 and R_2 together form a 6-member ring with NR_{11} at the 4-position of the 6-member ring.

16. A method according to claim 6 wherein Y is $(CH_2)_3$; and R_1, R_2 and R_3 are each methyl.

17. A method according to claim 6 wherein Y is $(CH_2)_3$; and R_1 is benzyl, R_2 is methyl and R_3 is methyl.

18. A method of treating a patient with a *M. tuberculosis* infection comprising administering to the patient an amount of a composition comprising a first inhibitor in combination with a second inhibitor, wherein said first inhibitor is administered in amounts effective to inhibit an electron transport system in said *M. tuberculosis* but wherein said amount is not effective as an anti-dopaminergic in said patient, and wherein said second inhibitor is a traditional anti-tuberculosis medicament.

19. The method of claim 18 wherein the second inhibitor is isoniazid, rifampin, streptomycin, pyrazinamide or ethambutol.

20. The method of claim 18 wherein said first and second inhibitors each has an IC50 greater than 100 μM in a D2 dopamine receptor binding assay.

21. The method of claim 18 wherein said first and second inhibitors each has an IC50 greater than 300 μM in a D2 dopamine receptor binding assay.

22. The method of claim 18 wherein said first and second inhibitors each has an IC50 less than 100 μM in an electron transport system model.

23. The method of claim 18 wherein said first and second inhibitors each has an IC50 less than 30 μM in an electron transport system model.

24. The method of claim 18 wherein said first and second inhibitors each has an IC50 less than 30 μM in an electron transport system model and an IC50 greater than 100 μM in a D2 dopamine receptor binding assay.

25. A method of modulating Type II NADH dehydrogenase in *M. tuberculosis* comprising contacting said cell with an amount of a composition comprising a *M. tuberculosis* modulator, said amount effective to inhibit an electron transport chain in said *M. tuberculosis* by at least 50%.

26. A method of protecting an animal from a *M. tuberculosis* infection comprising administering to said animal an amount of a composition comprising a *M. tuberculosis* electron transport chain polypeptide modulator effective to inhibit the electron transport chain in *M. tuberculosis.*

27. A method of modulating respiration in a pathogen comprising administering to said pathogen an amount of a composition comprising a modulator effective to inhibit the electron transport chain in *M. tuberculosis.*

28. A method of modulating replication in a pathogen comprising administering to said pathogen an amount of a composition comprising a modulator effective to inhibit the electron transport chain in *M. tuberculosis.*

29. A method of modulating growth of a pathogen comprising administering to said pathogen an amount of a composition comprising an modulator effective to inhibit the electron transport chain in *M. tuberculosis.*

30. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein inhibition of the electron transport chain is detected by measuring one or more of: oxidation of NADH, growth inhibition of *M. tuberculosis* or *M. smegmatis*, inhibition of respiration of *M. tuberculosis* or *M. smegmatis*, or inhibition of replication of *M. tuberculosis* or *M. smegmatis.*

31. The method of claim 30 wherein inhibition is at least 50% as compared to a control.

32. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein the electron transport chain is inhibited by inhibiting one or more type II NADH dehydrogenase, menaquinone, flavin adenine dinucleotide, bc1 complex, cytochrome bd oxidase, fumarate reductase, or nitrate reductase.

33. The method of claim 32 wherein the type II NADH dehydrogenase is type II NADH dehydrogenase *ndh* or type II NADH dehydrogenase *ndhA*.

34. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said effective amount inhibits the electron transport system in *M. tuberculosis* and does not have extrapyramidal side effects in said patient.

35. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 said effective amount inhibits the electron transport system in *M. tuberculosis* and does not block dopamine receptors.

36. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor exhibits reduced side effects compared to treatment with a composition having anti-dopaminergic effects.

37. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein the patient has not been diagnosed as having one or more psychological diseases or disorders at the time of treatment.

38. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein the patient is not classified as psychotic according to the criteria of DSM-IV.

39. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said composition is effective at a concentration of less than about 10 μM to inhibit electron flow by at least 50% in an *in vitro* assay of electron transport.

40. The method any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor is not chlorpromazine or trifluperazine.

41. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor is an antibody selective for a *M. tuberculosis* electron transport chain polypeptide.

42. The method of claim 4a wherein said *M. tuberculosis* electron transport chain polypeptide has an amino acid sequence of SEQ ID NO:1, 3, 5, 7, 9 or 11.

43. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said *M. tuberculosis* is resistant to one or more of isoniazid, rifampin, streptomycin, pyrazinamide and ethambutol.

44. The method of claim 34 or 36 wherein said side-effects are selected from the group consisting of Dystonia, drooling, tremors, Tardive diskensia, Neuroleptic Malignant Syndrome (NMS), hyperpyrexia, muscle rigidity, altered mental status, autonomic instability (irregular pulse, abnormal blood pressure, tachycardia, disphoresis), anemia, jaundice,

diminishing the effect of oral anti-coagulants, causes chromosomal abberations in rodents, drowsiness, dizziness, skin reaction, rash, dry mouth, insomnia, amenorrhea, fatigue, muscle weakness, anorexia, lactation, blurred vision, motor restlessness, spasms, and neuromuscular reaction.

45. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein the inhibitor is an antisense oligonucleotide comprising at least 80% sequence homology to the complement of a nucleic acid molecule encoding a *M. tuberculosis* electron transport chain polypeptide (SEQ ID NO:2, 4, 6, 8, 10 or 12), wherein said antisense oligonucleotide specifically hybridizes to the nucleic acid molecule and inhibits *M. tuberculosis* electron transport chain polypeptide mRNA levels by at least 50% in *M. tuberculosis*.

46. The method of claim 45 wherein said antisense oligonucleotide specifically hybridizes with the 5' UTR, start codon region, intron/exon region, coding region, stop codon region, or 3'UTR of said polynucleotide.

47. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein the antisense oligonucleotide comprises at least 95% sequence homology to the complement of a nucleic acid molecule encoding *M. tuberculosis* electron transport chain polypeptide (SEQ ID NO:2, 4, 6, 8, 10 or 12).

48. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor is an antisense oligonucleotide specifically hybridizable to an electron transport chain polynucleotide, wherein said electron transport chain polynucleotide is type II NADH dehydrogenase, menaquinone, flavin adenine dinucleotide, bc1 complex, cytochrome bd oxidase, fumarate reductase, or nitrate reductase.

49. The method of claim 45 wherein said antisense oligonucleotide inhibits *M. tuberculosis* electron transport chain polypeptide mRNA levels by at least 75% in *M. tuberculosis*.

50. The method of claim 45 wherein said antisense oligonucleotide inhibits *M. tuberculosis* electron transport chain polypeptide mRNA levels by at least 90% in *M. tuberculosis*.

51. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 further comprising administering to said patient a composition comprising one or more of isoniazid, rifampin, streptomycin, pyrazinamide or ethambutol.

52. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor has an IC50 greater than 100 μM in a D2 dopamine receptor binding assay.

53. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor has an IC50 greater than 300 μM in a D2 dopamine receptor binding assay.

54. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor has an IC50 less than 100 μM in an electron transport system model.

55. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor has an IC50 less than 10 μM in an electron transport system model.

56. The method of any one of claim 1, 18, 25, 26, 27, 28 or 29 wherein said inhibitor has an IC50 less than 10 μM in an electron transport system model and an IC50 greater than 100 μM in a D2 dopamine receptor binding assay.

57. An isolated polypeptide comprising a fragment of an electron transport chain polypeptide, said fragment at least 10 amino acid residues and comprising at least one epitope of the electron transport chain polypeptide.

58. The polypeptide of claim 57 wherein said electron transport chain polypeptide is a *M. tuberculosis* or *M. smegmatis* electron transport chain polypeptide.

59. The polypeptide of claim 57 comprising a sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11.

60. The polypeptide of claim 58 wherein said polypeptide is from about 8 to about 20 amino acids in length.

61. The polypeptide of claim 57 wherein said polypeptide binds specifically to an anti-type II NADH dehydrogenase antibody.

62. An isolated epitope-bearing fragment of the polypeptide comprising a sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11, said fragment having at least 10 amino acid residues.

63. The epitope-bearing fragment of claim 62, which comprises between about 6 and about 20 contiguous amino acids of SEQ ID NO: 1, 3, 5, 7, 9 or 11.

64. The epitope-bearing fragment of claim 63, which consists of about 10 contiguous amino acids of SEQ ID NO: 1, 3, 5, 7, 9 or 11.

65. An isolated anti-electron transport chain polypeptide antibody obtained by immunization of a subject with the epitope-bearing fragment of claim 63.

66. An isolated anti-electron transport chain polypeptide antibody, wherein said antibody recognizes at least one region of an electron transport chain polypeptide comprising a sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11.

67. The isolated anti-electron transport chain polypeptide antibody of claim 66, wherein said antibody binds to a catalytic, hydrolytic or binding region of an electron transport chain polypeptide.

68. The antibody of claim 66 wherein said electron transport chain polypeptide is a *M. tuberculosis* or *M. smegmatis* electron transport chain polypeptide.

69. The antibody of claim 66 wherein said antibody is a monoclonal antibody.

70. The antibody of claim 66 wherein said antibody is a polyclonal antibody.

71. The antibody of claim 66 wherein said antibody is a chimeric antibody.

72. The antibody of claim 66 wherein said antibody is a humanized antibody.

73. The antibody of claim 66 wherein said antibody is a single-chain antibody.

74. The antibody of claim 66 wherein said antibody is a Fab fragment.

75. The antibody of claim 66 wherein said antibody is labeled.

76. The antibody of claim 75 wherein said label is an enzyme, radioisotope, or fluorophore.

77. The antibody of claim 66 wherein the binding affinity of said antibody is less than about
1×10^5 K_a for a polypeptide other than an electron transport chain polypeptide.

78. An isolated cell that produces the antibody of claim 66.

79. A hybridoma that produces the antibody of claim 66.

80. A composition comprising the anti-electron transport chain polypeptide antibody of claim 66 and a pharmaceutically acceptable carrier.

81. A method of treating a tuberculosis patient comprising administering to said patient a therapeutically effective amount of the antibody of claim 66.

82. An immunogenic composition comprising a polynucleotide encoding a *M. tuberculosis* electron transport chain polypeptide, or immunogenic fragment thereof, said fragment having at least 10 amino acid residues.

83. The immunogenic composition of claim 82 wherein said polynucleotide has the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10 or 12.

84. An immunogenic composition comprising a *M. tuberculosis* electron transport chain polypeptide, or immunogenic fragment thereof, said fragment having at least 10 amino acid residues.

85. The immunogenic composition of claim 84 wherein said *M. tuberculosis* electron transport chain polypeptide is at least a fragment of a protein having the amino acid sequence of SEQ ID NO:1, 3, 5, 7, 9 or 11.

86. A composition comprising a recombinant vaccine comprising a nucleotide sequence that encodes a *M. tuberculosis* electron transport chain polypeptide, or immunogenic fragment thereof having at least 10 amino acid residues, operably linked to regulatory elements.

87. The composition of claim 86 wherein said immunogen is at least an immunogenic portion of a protein having the amino acid sequence of SEQ ID NO:1, 3, 5, 7, 9 or 11.

88. The composition of claim 86 wherein said recombinant vaccine is a recombinant vaccinia vaccine.

89. A composition comprising a live attenuated pathogen comprising a nucleotide sequence that encodes one or more *M. tuberculosis* electron transport chain polypeptides or functional fragments thereof, said fragments having at least 10 amino acid residues.

90. The composition of claim 89 wherein the functional fragment is immunogenic.

91. An injectable pharmaceutical composition comprising the compositions of any one of claims 82-90.

92. A pharmaceutical dosage form comprising the compositions of any one of claims 82-90.

93. The pharmaceutical dosage form of claim 92 wherein said pharmaceutical dosage form is a solid dosage form is selected from the group consisting of tablets, caplets, beads, or capsules.

94. The pharmaceutical dosage form of claim 92 wherein said pharmaceutical dosage form is a liquid dosage form is selected from the group consisting of a syrup, elixir, solutions or suspension.

95. A method of immunizing an individual against *M. tuberculosis* comprising administering to said individual the composition of any one of claims 92, 93 or 94.

96. A method of immunizing an individual against a pathogen comprising administering to said individual the composition of claim 89.

97. A method of inducing an immune response in an individual against *M. tuberculosis* comprising administering to said individual the composition of claim 86.

98. The method of any one of claims 1, 18, 25, 26, 27, 28 or 29 wherein the *M. tuberculosis* is in a dormant state.

99. A method for detecting the presence of *M. tuberculosis* in a sample comprising: contacting the sample with an electron transport chain inhibitor comprising a detectable label and detecting evidence of the electron transport chain inhibitor in said sample, wherein evidence of the electron transport chain inhibitor is indicative of the presence of *M. tuberculosis*.

100. The method of claim 99 wherein said sample is a human sample.

101. The method of claim 99 wherein said detecting comprises comparing the results of said contacting with a control.